REMARKS/ARGUMENTS

STATUS OF THE CLAIMS

Claims 1-19, 21-61, and 201-221 are pending with entry of this amendment, claims 201-221 having been withdrawn and claims 20, 62-200, and 222-303 having been cancelled. Claims 21, 29, 36, and 45 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

Applicants note with appreciation the Examiner's indication of allowable subject matter. The Action indicated that claims 21-46 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Accordingly, claims 21, 29, 36, and 45 have been amended as suggested by the Examiner. Claims 21, 29, and 36 have been rewritten in independent form to include the limitations of base claims 1 and 2 and intervening claim 18. Claim 45 has been rewritten in independent form to include the limitations of base claims 1 and 2.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

The Action noted that claims 12 and 14-17 are withdrawn as being drawn to non-elected species. However, pursuant to MPEP 803.02, claims to non-elected species are held to be withdrawn if on examination the elected species is found to be anticipated or rendered obvious by prior art; otherwise, the Examiner's search is to be extended. Applicants therefore do not consider claims 12 and 14-17 to be withdrawn.

Applicants further note that, as indicated in the response to the restriction requirement filed March 3, 2005, claims 14-17 read on the elected species.

The action of December 16, 2005 included: rejections for alleged indefiniteness (item 4), rejections for alleged anticipation (item 5), rejections for alleged obviousness (items 6-8), and indication of allowable subject matter (items 12-13). Applicants traverse all rejections and

objections, to the extent that they may be applied to the amended claims, for the reasons noted herein.

THE INFORMATION DISCLOSURE STATEMENT

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement submitted on September 22, 2005.

THE CLAIMS ARE FREE OF BARRETT (ACTION ITEM 5)

Claims 2 and 57-60 were rejected for alleged anticipation under 35 USC 102(b) by Barrett et al. Applicants respectfully traverse these rejections.

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention.

Barrett et al. describe methods and compositions for immobilizing anti-ligands at predetermined positions on the surface of a solid substrate. According to Barrett et al., caged binding members are attached to the surface. The caging groups are removed from the caged binding members at predetermined regions on the surface, and anti-ligands are bound to the now uncaged binding members at the predetermined regions. The anti-ligands immobilized on the surface can then be used, for example, to detect ligand binding to the anti-ligands (summarized, e.g., in column 2 lines 38-68). The invention described by Barrett et al. simply does not correspond with a caged sensor for detecting an activity of an enzyme according to the present invention.

Applicants maintain that Barrett et al. do not specifically teach use of substrate/enzyme pairs as anti-ligand/ligand pairs. However, even if, *arguendo*, Barrett et al. describe substrate/enzyme pairs, Barrett et al. do not describe either a first label or first caging groups meeting the limitations of claim 2.

The Action alleges that Barrett et al. teach one or more caging groups associated with a molecule inhibiting an enzyme from acting on a substrate. The Action equates a ligand of Barrett et al. with an enzyme of the present invention, and an anti-ligand of Barrett et al. with a substrate of the present invention.

Applicants note that Barrett et al. teach caged binding members, which are uncaged to permit binding of the ligand (equated with the enzyme in the Action) to the binding member. Although the Action correctly notes that caging groups are not required to be on the substrate and must only be on the one or more molecules of the caged sensor, claim 2 requires that the caging groups inhibit the enzyme from acting on the substrate. The caging groups of Barrett et al. - which prevent binding of the ligand to the binding member - do not in any way affect binding of the ligand (equated with the enzyme) and its anti-ligand (equated with the substrate). The caging groups of Barrett et al. can not be construed as in any way inhibiting action of the enzyme on its substrate. Barrett et al. thus fail to teach first caging groups meeting the limitations of claim 2.

The Action also alleges that Barrett et al. teach "a first label, wherein a first signal is exhibited by the first label is when the substrate is in its first state (first state is unbound with no signal and second state is bound with a signal, col. 21, lines 36-44)." However, Applicants note that lines 36-44 describe binding of a labeled ligand to those anti-ligands on the surface having high affinity for the ligand. The Action considers the first state to be where the ligand (which the Action equates with an enzyme) is not bound to the anti-ligand (which the Action equates with a substrate) and the second state to be where the ligand is bound to the anti-ligand. This simply does not correspond with caged sensors as described in claim 2. In lines 36-44 from Barrett et al., the label is present on the surface if the ligand is bound to the particular anti-ligand and not present on the surface if the ligand is not bound - there is no dependence whatsoever of the signal from the label on the state of the anti-ligand. Indeed, Barrett et al. do not describe modification or potential modification of the anti-ligand by the ligand, merely binding, and as such do not teach a second state of the anti-ligand produced by action of the ligand. Barrett et al. completely fail to teach a first label wherein a first signal from the label when the substrate is in the first state is distinguishable from a second signal from the label when the substrate is in its second state, as is required by claim 2.

Additional points of distinction are present in the dependent claims, but because independent claim 2 is not anticipated, it is not necessary to address each additional point.

Barrett et al. do not teach at least a first label whose signal is responsive to the state of the substrate or one or more caging groups that inhibit the enzyme from acting on the substrate. Barrett et al. thus fail to teach a caged sensor including a substrate and a first label that meets the limitations recited in the claims. The rejections must be withdrawn.

THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 6-8)

Item 6

Claims 1-11 and 18 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. Applicants respectfully traverse these rejections.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims (M.P.E.P § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (M.P.E.P. § 2143.01). Third, a reasonable expectation of success is required (M.P.E.P. § 2143.02). The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (M.P.E.P. §2143).

The combination of Glickman et al. and Burbaum et al. does not meet the requirements for a *prima facie* case of obviousness. First, the combination does not teach all the limitations of the claims. For example, the combination does not teach at least a first label meeting the limitations of claim 1 or claim 2, or a cell comprising a caged sensor meeting the limitations of claim 1.

Glickman et al. teach a method for measuring tyrosine kinase activity in which tyrosine-phosphorylated substrates are captured on a solid support coated with a first anti-phosphotyrosine antibody. A second anti-phosphotyrosine antibody, which is labeled, is then bound to the phosphorylated substrates captured on the support, capturing the second labeled antibody on the support. Unbound second labeled antibody is removed, and the amount of second labeled antibody bound to the solid support is measured. Glickman et al. thus describe an assay that relies on capture on a solid support. The label on the second antibody exhibits the same signal regardless of the phosphorylation state of the substrate.

The label is not responsive to the state of the substrate; it is merely either bound or not bound to the solid support.

Glickman et al. thus fail to teach a first label that exhibits a first signal when the substrate is in its first state and a second, distinguishable signal when the substrate is in its second state, as is specified in claims 1 and 2. Merely adding the caging group from the caged substrate of Burbaum et al. does not result in the claimed invention; the combination still fails to teach a first label whose signal is responsive to the state of the substrate.

With respect to claim 2, Glickman et al. also fail to teach a cell comprising the sensor. The Action appears to equate a substrate and a labeled anti-phosphotyrosine antibody of Glickman et al. with a sensor of the present invention. Even if the substrate plus labeled antibody were equivalent to a sensor of the present invention, which as noted above Applicants do not concede, the substrate and labeled antibody of Glickman are not present in a cell. Although the substrate may initially be inside a cell, it is removed from the cell for binding to the solid support and contact with the labeled antibody - the labeled antibody is not present in the cell. See, e.g., column 5 line 24-column 6 line 22.

Since Glickman et al. fail to teach a cell comprising a sensor (both because the substrate and labeled antibody of Glickman are not both present in a cell and because the substrate and labeled antibody do not comprise a sensor), merely adding the caging group from the caged substrate of Burbaum et al. to the substrate and labeled antibody of Glickman does not result in a cell comprising a caged sensor such as that specified in claim 2.

Additional points of distinction are present in the dependent claims, but because independent claims 1 and 2 are not anticipated, it is not necessary to address each additional point.

However, with respect to claim 9, Applicants note that the substrate and label (on the anti-phosphotyrosine antibody) of Glickman et al. are not, as the Action alleges, physically connected. The substrate and the labeled antibody of Glickman et al. are two discrete molecules, not joined by a linker or any other physical connection. Glickman et al. thus fail to teach the first label and the substrate being physically connected.

With respect to claims 3-5, the Action alleges that "the claims are drawn to intended use of the composition and do not appear to require any further physical

limitations." Applicants note that claim 3 provides several exemplary percentages by which the caging groups can inhibit the enzyme from acting on the substrate, while claim 4 indicates that in certain embodiments the caging groups prevent the enzyme from acting on the substrate. Claims 1 and 2 cover embodiments in which the caging groups inhibit the enzyme from acting on the substrate - which includes subsets of embodiments in which the caging groups inhibit by certain percentages and in which the caging groups prevent the enzyme from acting on the substrate. Claims 3 and 4 simply specify products that fall into these subsets, by specifying that the caging groups possess certain physical properties. Similarly, claim 5 specifies that the caging groups possess certain physical properties: removal of the caging groups can permit the enzyme to act upon the substrate, or an induced conformational change in the caging groups can permit the enzyme to act upon the substrate. Claims 3-5 thus specify physical properties of the composition; they are not drawn to intended uses of the composition.

The combination of Glickman et al. and Burbaum et al. does not teach all the limitations of the claims. Specifically, at least the following limitations are simply not taught by the combination: a first label whose signal is responsive to the state of the substrate, and a cell comprising a caged sensor. Furthermore, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. The rejections should be withdrawn.

Item 7

Claims 13, 19, and 61 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. further in view of Kris et al. Applicants respectfully traverse these rejections.

The combination of Glickman et al., Burbaum et al., and Kris et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims.

As described above, the combination of Glickman et al. and Burbaum et al. fails to teach all the limitations of claims 1 and 2, from which the claims at issue depend. For example, the combination of Glickman and Burbaum fails to teach at least a first label and a

cell comprising a caged sensor. Merely adding instructions for use in a kit or the identity of the enzyme as a protease from Kris et al. does not result in the claimed invention; the combination still fails to teach a first label whose signal is responsive to the state of the substrate or a cell comprising a caged sensor.

Regarding claim 19, Kris et al. is alleged to "teach a polypeptide substrate (par. 18-19) wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and first label, par. 256-258)." Applicants note, however, that the substrate and the antibody are in fact two separate molecules. The fact that the labeled antibody can bind the phosphorylated substrate does not mean that the antibody and substrate are on a single polypeptide; whether they are bound to each other or not, they are still two distinct polypeptides.

Also regarding claim 19, the Action alleges that the first label is located at the tyrosine residue. However, Applicants note that the label of Kris et al. is located on the antibody; the label not found on the substrate at all, much less at the tyrosine residue of the substrate. Furthermore, although the Action alleges that the label "exhibits a first signal when the residue is not phosphorylated and the second signal when the" residue is phosphorylated, Applicants note that the signal from the label is not actually responsive to the state of the substrate. Kris et al. teach a capture assay, in which labeled antibody binds to substrate on a solid support if the substrate is phosphorylated. The label on the antibody exhibits the same signal regardless of the phosphorylation state of the substrate. The label is not responsive to the state of the substrate; it is merely either bound or not bound to the solid support. Kris et al. thus fail to teach a label that exhibits a first signal when the substrate is not phosphorylated and a second signal when the substrate is phosphorylated.

The combination of Glickman et al., Burbaum et al., and Kris et al. thus does not teach all the limitations of the claims. For example, it fails to teach at least a first label whose signal is responsive to the state of the substrate (specifically, the phosphorylation state), a cell comprising a caged sensor, and a single polypeptide including the substrate and first label. Moreover, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no

reasonable expectation of success, since the suggested combination does not result in the present invention. The rejections should be withdrawn.

Item 8

Claims 47-49 and 52-54 were rejected for alleged obviousness under 35 USC 103(a) over Glickman et al. in view of Burbaum et al. further in view of Fischer et al. Applicants respectfully traverse these rejections.

The combination of Glickman et al., Burbaum et al., and Fischer et al. does not meet the requirements for a *prima facie* case of obviousness. For example, the combination does not teach all the limitations of the claims.

As described above, the combination of Glickman et al. and Burbaum et al. fails to teach all the limitations of claims 1 and 2, from which the claims at issue depend. For example, the combination of Glickman and Burbaum fails to teach at least a first label and a cell comprising a caged sensor. Merely adding a cellular or subcellular delivery module from Fischer et al. does not result in the claimed invention; the combination still fails to teach a first label whose signal is responsive to the state of the substrate or a cell comprising a caged sensor.

In addition, motivation to combine the teachings of the references is lacking. No suggestion to combine the teachings is found in the references. In addition, there is no reasonable expectation of success, since the suggested combination does not result in the present invention. The rejections should be withdrawn.

THE CLAIMS, AS AMENDED, ARE DEFINITE (ACTION ITEM 4)

35 USC §112, Paragraph 2 Rejection of Claims 1-11, 13, and 18-61

Claims 1-11, 13, and 18-61 were rejected for alleged indefiniteness because it was allegedly unclear whether the first caging groups are considered part of the first state of the substrate, whether an enzyme is required as part of the composition, and, if not, how the substrate can be converted into a second state from the first state. Applicants respectfully traverse these rejections.

The claims were rejected because it was allegedly unclear whether the first caging groups are considered part of the first state of the substrate. A complete reading of claims 1 and 2 and of the specification, e.g., at paragraphs 198, 199, and 204, makes it clear

that the caged sensor includes a) one or more molecules comprising the substrate, wherein the substrate is in a first state, and b) one or more first caging groups associated with the one or more molecules. The caging groups are thus clearly not considered to be part of the first state of the substrate. Accordingly, there is nothing indefinite about the phraseology at issue.

The Action further alleges that "it is unclear whether the caging group is associated with the first state of the enzyme substrate or whether the caging groups are present in the composition when the substrate is in the first and second states." Claims 1 and 2, and the corresponding paragraphs in the specification, indicate that the first caging groups are associated with the one or more molecules comprising the substrate in the first state; thus, the first caging groups can be associated with the first state of the substrate. Applicants note that whether the first caging groups are also associated with the second state of the substrate is irrelevant to these claims. However, as explicitly indicated throughout the application, in some embodiments the first caging groups are also associated with the second state of the substrate, while in other embodiments the first caging groups are not physically associated with the second state of the substrate. See, for example, claim 5, which indicates that either removal of, or an induced conformational change in, the first caging groups permits the enzyme to act upon the substrate thus converting it to the second state. In embodiments in which the first caging groups are removed before the enzyme acts on the substrate, the caging groups are not associated with the second state of the substrate. (See, e.g., the description of photolabile caging groups at paragraphs 152 and 209 or the schematic illustrations in Figures 6-11.) In contrast, in some (though not all) embodiments in which the caging groups undergo a conformational change to permit the enzyme to act on the substrate, the caging groups remain associated with the substrate and are thus associated with the second state. (See, e.g., the covalently associated polymer caging groups at the end of paragraph 355, shown schematically in Figure 58.) Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

The claims were also rejected because it was allegedly unclear whether an enzyme is required as part of the composition. As the Action correctly notes, claims 1 and 2 do not specifically claim an enzyme. There is thus no requirement that the enzyme be part of the composition comprising the caged sensor. The enzyme is optionally present (see, e.g.,

claim 11). The Action further alleges that if "the enzyme is not required as part of the composition, it is unclear how the substrate can be converted into a second state from a first state." Applicants note that claims 1 and 2 do not require that the substrate be converted from the first state to the second state; the claims specify that the substrate is in the first state, and that the first state is one on which the enzyme can act to convert the substrate to the second state. Applicants note that a compound known to be a substrate for a particular enzyme is readily recognized as such, regardless of whether the enzyme is present. Accordingly, there is nothing indefinite about the phraseology at issue, and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing, Applicant(s) believe(s) all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, **an interview with the Examiner is hereby requested**. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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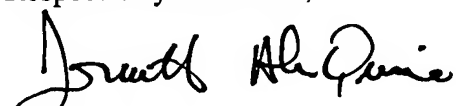
Respectfully submitted,



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Attachments:

1) A petition to extend the period of response for one months;
2) A transmittal sheet; and,
3) A receipt indication postcard.